REMARKS

Of the 30 original claims, claims 1, 19, 23 and 26 are amended. Claims 2-18, 20-22, 24, 25 and 27-30 have been cancelled. New, dependent claims 31-40 have been added. With this response, claims 1, 19, 23, 26, and 31-40 are now pending.

Support for the amendments to claims 1, 19 23 and 26, as well as newly added claim 35, can be found in the specification as filed, as well as in the claims as originally filed, especially on pages 40-41 wherein probucol derivatives (esters) are described for use in the invention. Support for new claims 31-40 can be found on pages 43-46 of the specification, especially on page 45, lines 9-13.

In a separate petition for an extension of time, Applicant has requested and paid the $475.00 small entity fee for securing a three-month extension of time for response. However, should the check be insufficient or not included, Applicant authorizes the Commissioner to deduct any fees relating to this document required under 37 C.F.R. §§ 1.16 to 1.21 from King & Spalding, LLP Deposit Account No. 11-0980, referencing matter number ATH 108 CON1.

I. Rejection under 35 U.S.C. § 102

A. Claims 1, 2, and 26 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Cheng, *et al.*, *Cancer Letters*, Vol 51(3), pp. 213-220 (1990) (hereinafter "Cheng"). The Examiner states that Cheng teaches the ability of antioxidants such as glutathione and Vitamin E to decrease cellular toxicity resulting from the administration of the antineoplastic cancer drug MGBG (methylglyoxal bis(guanylhydrazone)) in both yeast and mammalian cells, which suggests that the concomitant administration of the MGBG with these antioxidants in mammalian drug therapy in order to decrease the antineoplastic drug toxicity is anticipated.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988). Further, inherent anticipation requires that the missing descriptive material is necessarily present, not merely probably or possibly present in the prior art. *In re Robertson*, 169 F.3d 743, 49 USPQ.2d 1949 (Fed. Cir. 1999).

Cheng is directed to examining what MGBG targets in yeast and Guinea pig keratinocyte cells, and examines the effect of certain antioxidants on reversing the drug toxicity associated with MGBG. Further, Cheng describes only the effect of the antioxidants Vitamin E, Vitamin C, and glutathione on reversing the drug toxicity associated with the use of MGBG.

Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. As Cheng does not describe the use of probucol esters for such a use, Applicant's present invention is not anticipated by Cheng.

Applicant respectfully requests that the rejections of claims 1, 2 and 26 under 35 U.S.C. § 102 be withdrawn.

B. Claims 1-2 and 26 were rejected under 35 U.S.C. § 102(a, b) as being allegedly anticipated by Ripoll, *et al.*, *J. Urology*, Vol. 136 (2), pp. 529-531 (1986) (hereinafter, "Ripoll"). The Examiner states that Ripoll teaches combining an antioxidant such as Vitamin E with an antineoplastic drug (e.g., adriamycin, ADR) in order to additively/synergistically enhance ADR's cytotoxicity while decreasing ADR-induced side effects such as toxicity.

Ripoll describes a study of the role of Vitamin E acid succinate in adjuvant chemotherapy with adriamycin on a variety of cancer cells *in vitro*. The results of this study reported in Ripoll shows that Vitamin E succinate, when administered with adriamycin, has a dual effect--the toxic effect observed in tumor cells is increased, and a protective effect in normal cells is observed, as evidenced by decreases in ID_{50}'s. However, no mention of the use of other agents, such as esters of probucol, are made.

As stated previously, Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. As Ripoll does not describe or suggest the use of probucol esters for such a use, Applicant's present invention is not anticipated by Ripoll.

Applicant respectfully requests that the rejections of claims 1, 2 and 26 under 35 U.S.C. § 102 be withdrawn.

C. Claims 1-2, 23 and 26 were rejected under 35 U.S.C. § 102(a, b) as being allegedly anticipated by Yasunaga, *et al.*, *Archiv. Fur Japnishe Chirurgie*, Vol. 52 (5), pp. 591-601 (1983) (hereinafter, "Yasunaga"). The Examiner states that Yasunaga teaches that antioxidants such as Vitamin E act not only as free radical scavengers to prevent cytotoxicity generated from the administration of antineoplastic agents that generate free radicals, but they also promote the antitumor effects of the agents, thus providing a teaching of administering an antioxidant and an antitumor agent to treat abnormally proliferating cells.

Yasunaga specifically addresses whether the co-administration of vitamin E can prevent the acute cardiotoxicity or immunosuppression induced by anticancer agents, regardless of

whether free radicals are produced or not. Three anti-cancer agents--adriamycin, mitomycin, and 5-FU--were coadministered with Vitamin E in mice. The results of the study showed that vitamin E protected against both immunosuppression and loss of spleen weight induced by the anticancer agents, and that the antitumor effects of the agents were promoted by the coadministration of vitamin E. However, Yasunaga makes no mention or suggestion of the use of esters of probucol to enhance the cytotoxic effects of the anticancer agents.

Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. As Yasunaga does not describe or suggest the use of probucol esters for such a use, Applicant's present invention is not anticipated by Yasunaga.

Applicant respectfully requests that the rejections of claims 1, 2, 23 and 26 under 35 U.S.C. § 102 be withdrawn.

D. Claims 1-2, 23 and 26 were rejected under 35 U.S.C. § 102(a, b) as being allegedly anticipated by Szczepanska, *et al.*, *Eur. J. Haematology*, Vol. 40 (1), pp. 69-74 (1988) (hereinafter, "Szczepanska"). The Examiner states that Szczepanska teaches that antioxidants protect against cytotoxic adverse effects of chemotherapeutics from different classes in *in vitro* human blood experiments, and therefore the reference provides a teaching of administering an antioxidant and an antitumor agent which would immediately anticipate the administration of the combined composition of the Applicant's invention.

Szczepanska describes the *in vitro* influence of several anticancer agents--namely adriblastine, hydroxyurea, methotrexate, 6-mercaptopurine, 5-FU, cytosine arabinoside, and nitrogen mustard--on the migration rate of human white blood cells when blood is incubated with

Vitamin E (α-tocopherol), Vitamin C (acetylosalicytic acid) or thiourea in order to examine the protective effect these latter three compounds may exert against drug-induced cytotoxicity. According to the results of the described experiments, the toxic effect of the drugs can be prevented by some or all of the compounds used in the study, although each exhibited a different "protection pattern" (see, page 72, column 2, paragraph 2). No mention or suggestion of the use of mono- or di-esters of probucol in reducing drug-induced cytotoxicity was made. Further, the compounds described are different chemically and structurally from the compounds described in Applicant's presently amended claims.

Claim 2 has been cancelled in the present communication. Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. Szczepanska does not describe the use of mono- or di-esters of probucol in order to enhance the cytotoxicity of anticancer drugs. Rather, Szczepanska describes only the use of Vitamin E, Vitamin C, and thiourea (which is not equivalent to probucol or esters of probucol) as detoxifying agents when co-administered with some antineoplastic drugs. Consequently, Szczepanska does not anticipate Applicant's currently pending claims, as amended.

Applicant respectfully requests that the rejections of claims 1-2, 23 and 26 under 35 U.S.C. § 102 be withdrawn.

E. Claims 2, 18, and 26 were rejected under 35 U.S.C. § 102(a, b) as being allegedly anticipated by Siveski-Iliskovic, *et al.*, *Circulation*, Vol. 91 (1), pp. 10-15 (1995) (hereinafter "Siveski-Iliskovic"). According to the Examiner, Siveski-Iliskovic teach the co-administration of probucol with adriamycin, an antineoplastic drug, in a mammal (rat) in order to treat the solid

growth of abnormally proliferating cells and to protect against the toxic side effects of adriamycin.

Siveski-Iliskovic describes the effects of probucol when it is co-administered with adriamycin in order to examine whether probucol affords protection against adriamycin-induced cardiomyopathy, and to determine whether probucol has an effect on the antitumor properties of adriamycin. Tests in rat models showed that while the co-administration of probucol and adriamycin did not significantly reduce the tumor size when compared to the administration of adriamycin alone (see, page 12, column 2, paragraph 1), the simultaneous treatment with probucol prevented or lowered the incidence of adriamycin-induced cardiomyopathic changes. As a result of these observations, Siveski-Iliskovic suggests that a combination therapy of probucol and adriamycin for the treatment of tumors would be warranted. However, no mention or suggestion of the use of mono- or di-esters of probucol for enhancing the cytotoxicity of an antineoplastic drug is made in this paper.

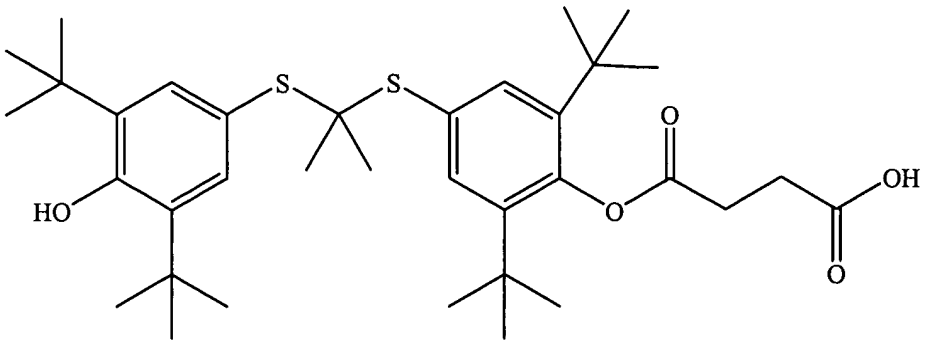
Claims 2 and 18 have been cancelled in the present communication. Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. Siveski-Iliskovic does not describe the use of mono- or di-esters of probucol in order to enhance the cytotoxicity of anticancer drugs. Rather, Siveski-Iliskovic describes only the use of probucol to reduce the incidence of adriamycin-induced cardiomyopathy when it is co-administered with adriamycin. Furthermore, Siveski-Iliskovic reports that the addition of probucol to adriamycin in combination therapy had no effect on the antitumor activity of adriamycin (see, page 14, column 2, paragraph 2). Consequently, Szczepanska does not anticipate Applicant's currently pending claims, as amended.

Applicant respectfully requests that the rejection of claims 2, 18 and 26 under 35 U.S.C. § 102 be withdrawn.

F. Claims 2, 23, and 26 were rejected under 35 U.S.C. § 102(a, b) as being allegedly anticipated by U.S. Patent No. 5,035,878 to Borch, *et al.* (hereinafter, "the '878 patent"). According to the Examiner, the '878 patent teaches the administration of dithiocarbamates to decrease the toxicity of antineoplastic drugs for the treatment of solid growth tumors.

The '878 patent is directed to dithiocarbamic compounds of the formula $[R^1R^2NC(=S)SM]$, for use in treating the toxic side effects of antineoplastic drugs such as DNA-synthesis inhibitors or alkylating 2-chloroethyl-containing drugs in mammals. According to the specification, R1 and R^2 are lower aliphatic , cycloaliphatic, heterocycloaliphatic, substituted or unsubstituted by hydroxyl, and M is H , a pharmaceutically acceptable cation, or $[-S-C(=S)NR^3R^4]$, wherein R^3 and R^4 are defined in the same manner as R^1 and R^2 (column 3, lines 24-47). No mention or suggestion of the use of esters of probucol are made in the '878 patent.

Claims 2 and 3 have been cancelled in the present response. Applicant's currently amended claims are directed to the use of mono- or di-esters of probucol to enhance the cytotoxicity of an antineoplastic drug in the treatment of a disorder of abnormal cellular proliferation. An exemplary compound has the general formula (I) shown below.



(I)

As is readily apparent, the compounds described in the currently amended claims are not equivalent to those compounds described in the '878 patent--e.g., there is no nitrogen. Consequently, because the '878 patent does not describe mono- or di-esters of probucol for use in enhancing the cytotoxicity of an antineoplastic drug, the '878 patent does not anticipate the presently claimed invention.

Applicant respectfully requests that the rejection of claim 26 under 35 U.S.C. § 102 be withdrawn.

II. Rejection under 35 U.S.C. § 103

Claims 1-3, 18, 19, 23 and 26 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Cheng in view of the American Heritage Dictionary of the English Language definition of "therapeutic index" (hereinafter "the therapeutic index definition"); over Ripoll in view of the therapeutic index definition; over Yasunaga in view of the therapeutic index definition; over Szczepanska in view of the therapeutic index definition; over Siveski-Iliskovic in view of the therapeutic index definition; and over the '878 patent in view of the therapeutic index definition. According to the Examiner, the "therapeutic index" is defined as "the ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment". Consequently, the Examiner states that one of ordinary skill in

the art would be motivated to utilize an antioxidant such as described in the cited art of reference with an antitumor agent in order to increase the therapeutic index of the antineoplastic agent.

According to MPEP § 706.02(j), for a claim to be obvious, there must be a) a suggestion or motivation to combine reference teachings, b) a reasonable expectation of success, and c) the references must teach all of the claim limitations, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Claims 2, 3 and 18 have been cancelled. Claims 1, 19, 23 and 26 have been amended with this communication to described ester of probucol in combination with antineoplastic drugs. None of the art cited by the Examiner suggests the use of mono- or di-esters of probucol to enhance the cancer cell cytotoxicity of an antineoplastic drug, or suggests combining their teachings. Similarly, none of the cited art suggests that the combination of mono- or di-esters of probucol with an antineoplastic drug would result in enhanced cytotoxicity of the drug. Further, the references, alone or in combination, do not teach all of the claim limitations of the presently pending claims 1, 19, 23, 26 and 31-40. Accordingly, Applicant requests that the rejections of claims 1-3, 18, 19, 23 and 26 under 35 U.S.C. § 103 be withdrawn.

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In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding objections and rejections are respectfully requested. All amendments are made in a good faith effort to advance the prosecution on the merits. The Examiner is encouraged to call the undersigned should any further action be required for allowance.

Respectfully submitted,

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